

Scientific Abstract:

Cancer is a leading cause of death in the Western World. Although most patients die from disseminated carcinoma, a substantial number die due to complications of locally advanced disease. Furthermore, patients who die of metastases frequently also suffer the morbidity of advanced local disease.

Current cancer therapy includes surgery, chemotherapy, and radiation therapy (RT). These treatment modalities, either alone or in combination, can provide high degrees of local control in early stage disease but often fail in eradicating bulky tumors or preventing metastatic disease. The local delivery of potent anti-tumor cytokines using gene transfer combined with currently available modalities provides the potential to enhance local control rates for a variety of tumor types.

Esophageal cancer, in particular, is highly lethal. The 5-year survival of all patient ranges from 2 to 10%. There are two standards of care for patients with localized disease, surgery alone, or concurrent chemotherapy and radiation (chemoradiation). At time of presentation, surgery is appropriate for about half of the patients who have localized disease, while the rest are not appropriate surgical candidates due to the presence of unresectable or metastatic disease or advanced comorbidities that preclude surgery. However, the five-year survival remains low even after surgical resection, with patients succumbing to local disease recurrence and/or distant metastases. Therefore there has been a high interest in combining preoperative treatments with surgery. The potential advantages of this approach include possibility that the tumor will be downstaged, the earlier treatment of micrometastases, a reduction in tumor seeding at surgery, and the ability to evaluate the effect of the preoperative interventions by pathologic examination of the surgical specimen (pathologic complete response, see below).

In this phase II protocol, we will combine TNFerade™, an adenoviral vector that expresses the human TNF- α gene, with preoperative chemoradiation. TNFerade™ contains genetic elements that are controlled by ionizing radiation up stream of the TNF- α gene. A practical aspect of this design is that expression of TNF can be spatially localized to injected and radiated tissue, thereby minimizing the risk of systemic toxicity.

The population for this study will be newly diagnosed adult subjects with locally advanced esophageal cancer (stage II and III) limited to the esophagus and regional lymph nodes who have not received prior treatment and are considered resectable. Patients will have histologically confirmed adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction. Patients with metastatic disease or patients with confirmed invasion of the bronchial tree or aorta at time of screening are not eligible.

The study will consist of two parts, a run-in dose-escalating phase (Part I) followed by a single arm phase (Part II). Although a favorable safety profile has been established with

TNFerade™ in the phase I studies, this cautious design has been chosen to provide additional safety data for TNFerade™ combined with chemotherapy and radiation in this specific indication. In Part I of the study, three doses, 4×10^8 particle units (pu), 4×10^9 pu, and 4×10^{10} pu of TNFerade™ will be administered in a dose-escalating fashion in up to 18 subjects (3-6/dose level). Following completion of this initial run-in phase, patients for Part II of the study will be assigned to chemoradiation with TNFerade™ at the maximally tolerated dose (MTD) or at a 4×10^{10} pu dose if the MTD is not reached. A two-stage Simon design will be employed for part II of the study. The pathologic complete response rate (pCR) rate will be determined after 26 patients have been treated at the MTD or 4×10^{10} pu dose. This is defined as the total absence of tumor in the resected tissue. If six or less patients show a pCR, the study will be stopped, as it is not likely that a significant increase in pCR rate will occur. If seven or more patients show a pCR, the study will continue to enroll a total of 53 patients at the MTD or 4×10^{10} pu. A complete response rate of 50% will be taken as evidence of activity.

Patients will undergo preoperative treatment consisting of chemoradiation [external radiation therapy (RT), fluorouracil (5-FU) and cisplatinol], combined with intratumoral injection of TNFerade™ biologic via endoscopic guided injection. Up to 5 weekly TNFerade injections will be administered as tolerated. TNFerade™ will be initiated on the same day that chemoradiation is started. Radiation therapy (RT) will be administered in 1.8 Gy daily fractions to a total dose of 45 Gy over 5 weeks. Chemotherapy will consist of cisplatinol/5-FU regimen with cisplatinol 75 mg/m^2 day 1 and day 22 and 5-FU $1000 \text{ mg/m}^2/\text{day}$ via continuous intravenous infusion for 96 hours starting day 1 and day 22 of RT. Patients will undergo total esophagogastrectomy at 4 to 10 weeks after completion of radiation. As described above, the primary endpoint will be pathologic complete response rate at esophagectomy. In addition, other study objectives include an assessment of time to disease progression, progression-free survival, median and one year survival, along with safety and tolerance.